Rapid diagnostics, and bugs and antibiotics: not that easy

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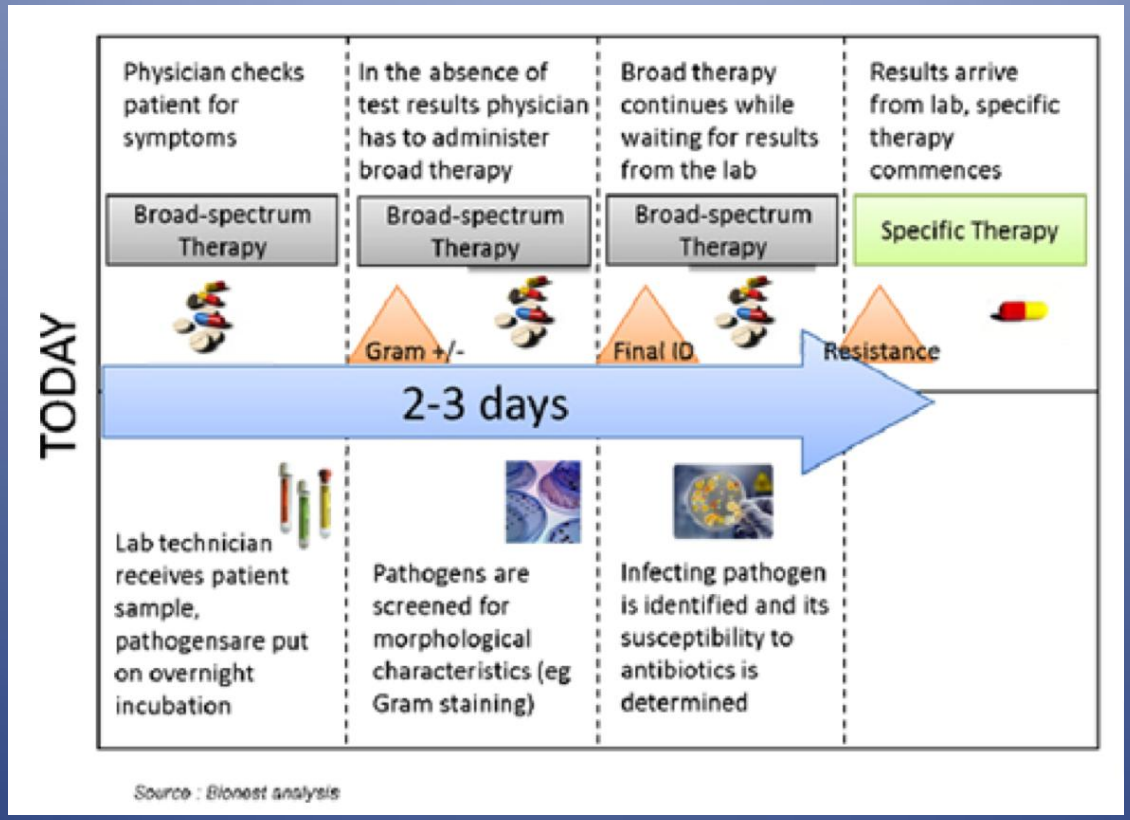
Declarations of interest

- Advisory panels
  - Astellas
  - Pfizer
  - MSD
  - Gilead
  - Cempra
- Instrument manufacturers
  - None
- Software manufacturers
  - None

The Need for Rapid Diagnosticszzzzzzzz.....



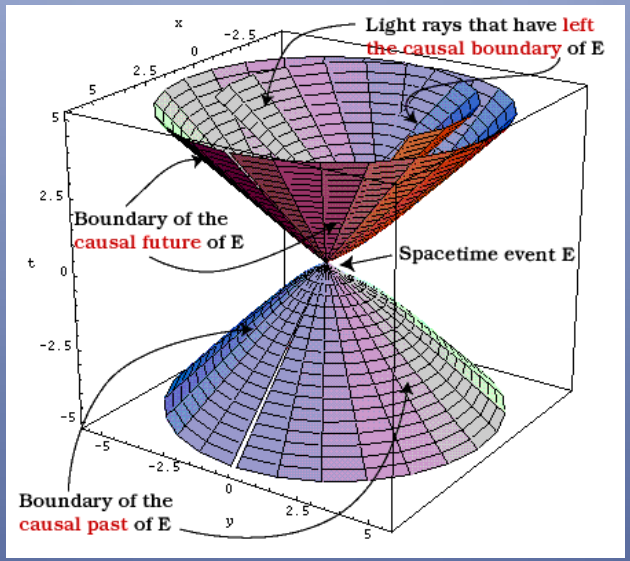
Potential Benefits of Rapid Diagnostics

- Improved, appropriate treatment and outcome for patient
- Improved infection control and outbreak monitoring
- Reduction in empirical antimicrobial prescriptions
  - Preservation of broad spectrum antimicrobials
  - Reduction in duration of treatment
  - Reduction in cost of treatment
  - Overall reduction antimicrobial consumption
  - Potential reduction in levels of resistance

Rapid diagnostics here often means… a molecular solution!

- FIND THAT BUG AND NAME IT QUICKLY
- NAME THAT ANTIBIOTIC RESISTANCE QUICKLY
- (*and hopefully*) DO THE RIGHT THING FOR THE PATIENT, QUICKER

Time is relative….



…and money

…and thought

Technology-driven solutions

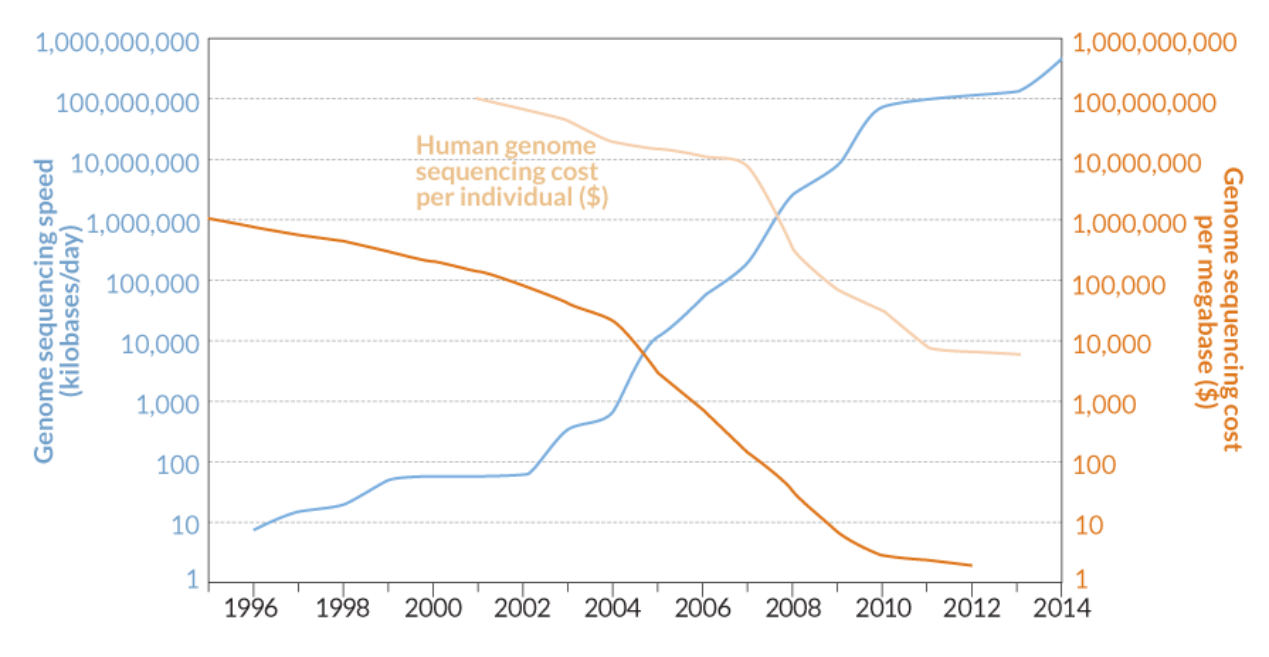
Sequencing speed

Sequencing chemistry

Microfluidics

Novel physics solutions

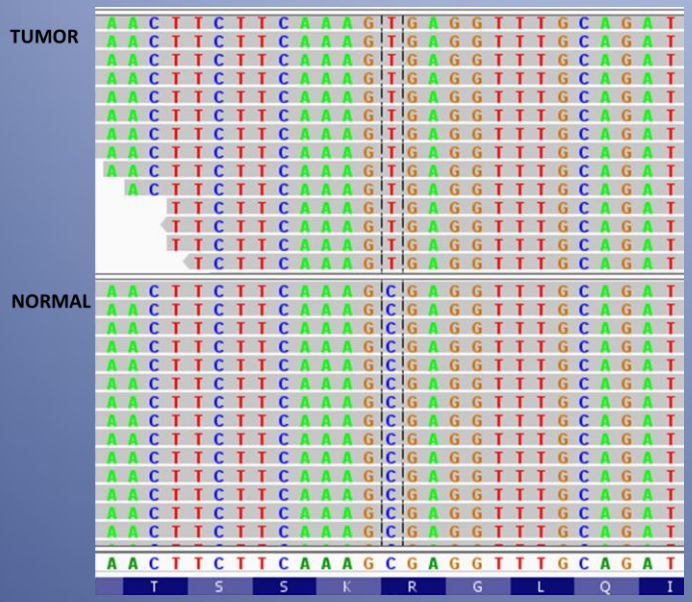
Mass production capability

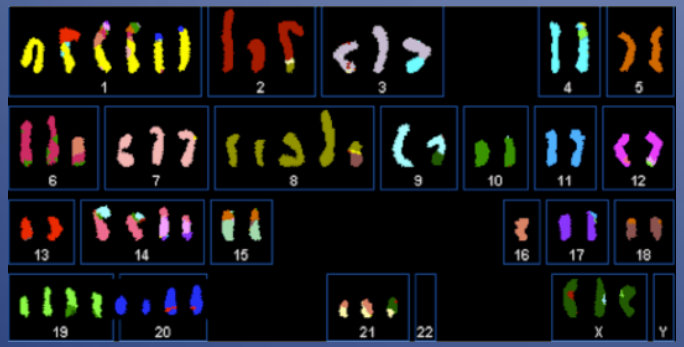


Human genome = one hour

In San Diego, a $207 million effort to deeply explore the health of 1 million patients is being led by Dr. Eric Topol, a Scripps Health cardiologist and geneticist

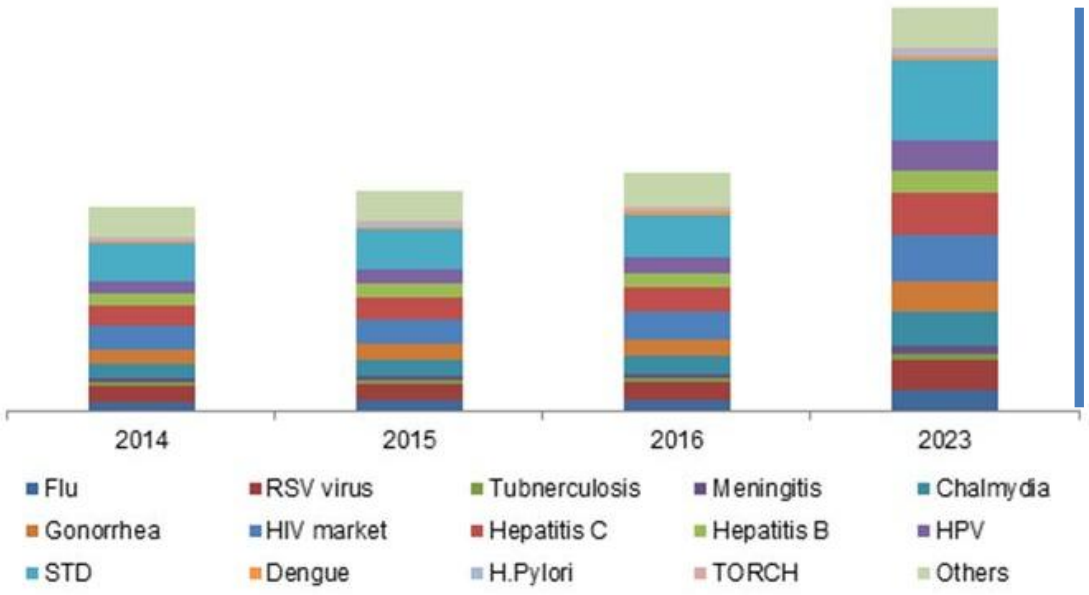
= $207 dollars per GWAS





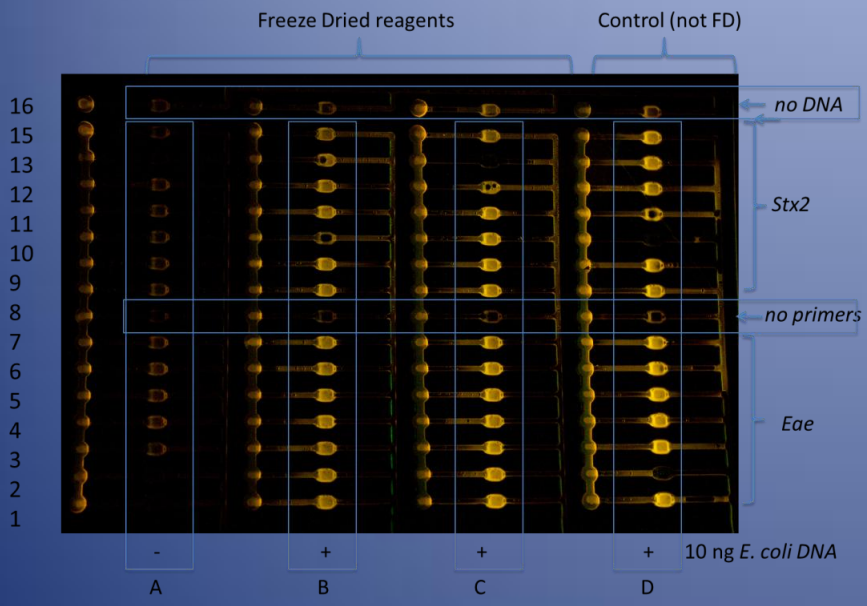
The technology's here.

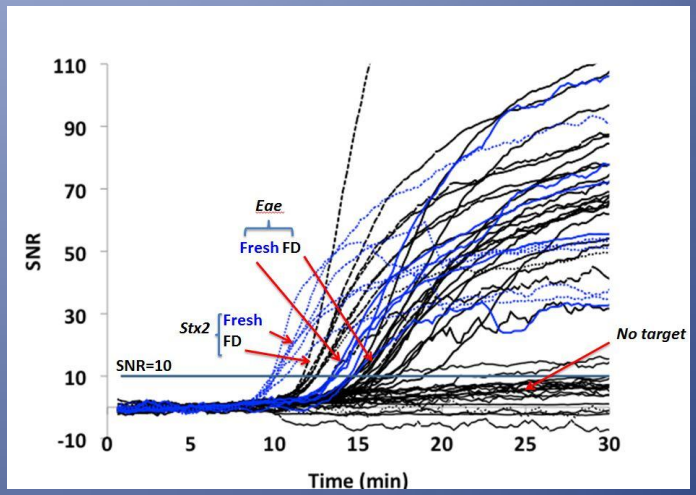
Molecular diagnostics market size, by infectious diseases, 2014 - 2023 (USD Million)



2000

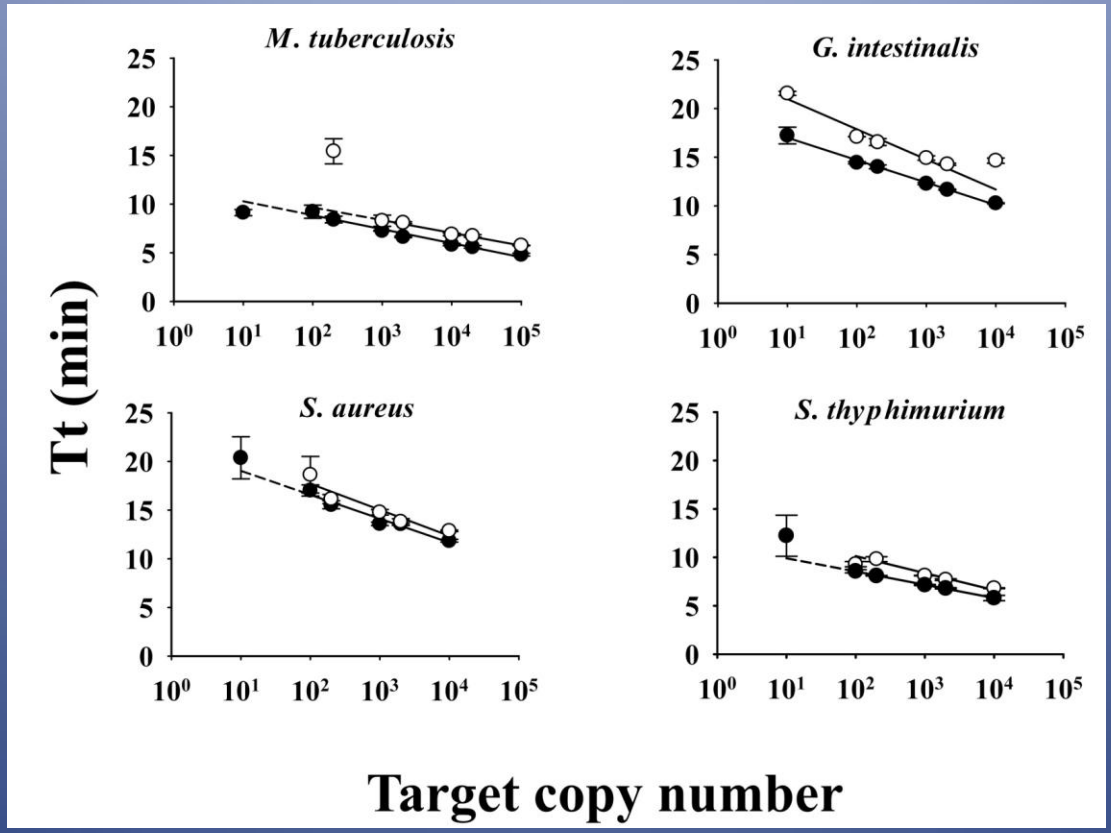
2. Simple: Dried Primers and Freeze Dried Reagents





Seyrig et al., 2011

10-min TB assay, for example!



Seyrig et al., 2011

PROBLEM NO. 1

Bacterial sepsis: the problem and the challenge

- 20 million cases per year worldwide
- 135000 deaths per year in Europe
- 21500 deaths a year in the USA

R^3 = Rapid, robust, reliable

Performance evaluation: ”first cut” output

n = 3318 samples	Prove-it™ Sepsis Positive	Prove-it™ Sepsis Negative	Accuracy
Reference method Positive	**1696** True positive	**94** False negative	**Sensitivity 95 %**
Reference method Negative/ positive*	**18** False positive†	**1476** True negative	**Specificity 99 %**

Tissari *et al:* Accurate and rapid speciation of bacteria from positive blood cultures using a novel DNA-based microarray platform.
Lancet 2010, 9719: vol 375

- Routine culture:
  - Average TAT: 57 hours

- Prove-it sepsis:
  - Average TAT (incl. week-end): 28 hours
  - Average TAT (excl. week-end): 17 hours

Articles

D-09-03605R1

S0140-6736(09)61569-5

Accurate and rapid identification of bacterial species from positive blood cultures with a DNA-based microarray platform: an observational study

Päivi Tissari, Alimuddin Zumla, Eveliina Tarkka, Sointu Mero, Laura Savolainen, Martti Vaara, Anne Aittakorpi, Sanna Laakso MSc, Merja Lindfors, Heli Piiparinen, Minna Mäki, Caroline Carder, Jim Huggett, Vanya Gant

How many were sold?

Why? because Doctors didn't need it.

"then…" = let's play safe and (we can afford to) wait for the cultures…..

PROBLEM NO. 1: NOT SOLVED.

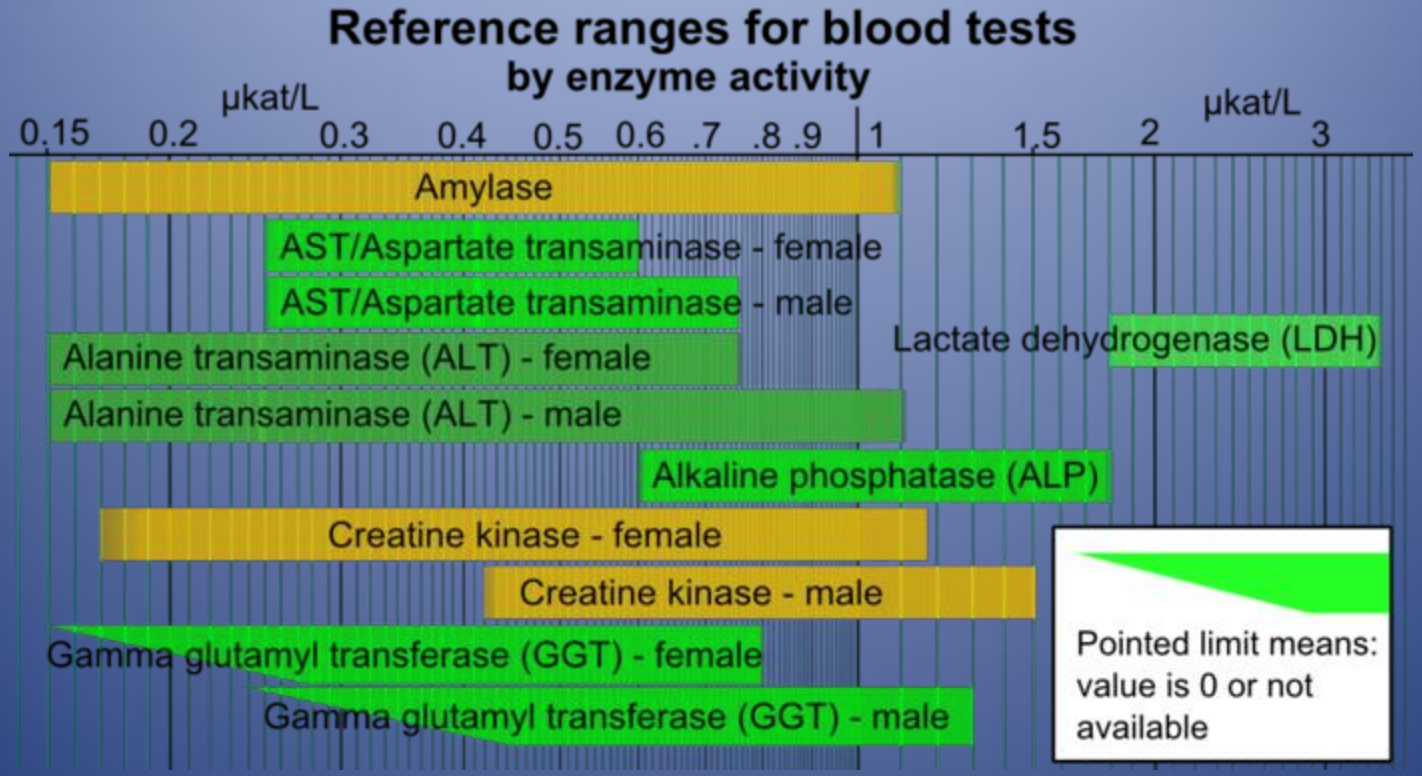
PROBLEM NO. 2

The serum Sodium is 138 mMol/L.
(normal range 132 – 145)

High!!!! DO *x*….

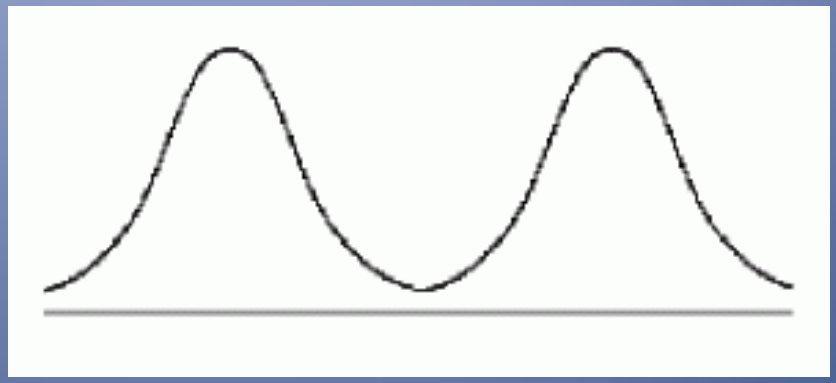
Normal!!!! DO nothing….

Low!!!! DO *y*….



Well ill

Frequency of bi-stable measurand



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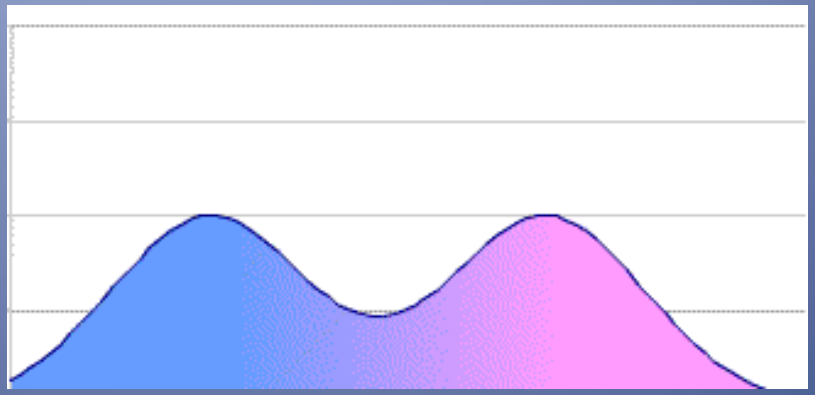
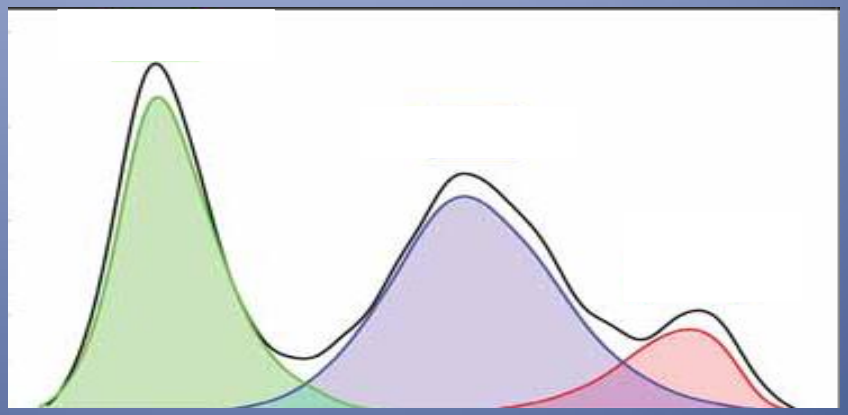


Well ill

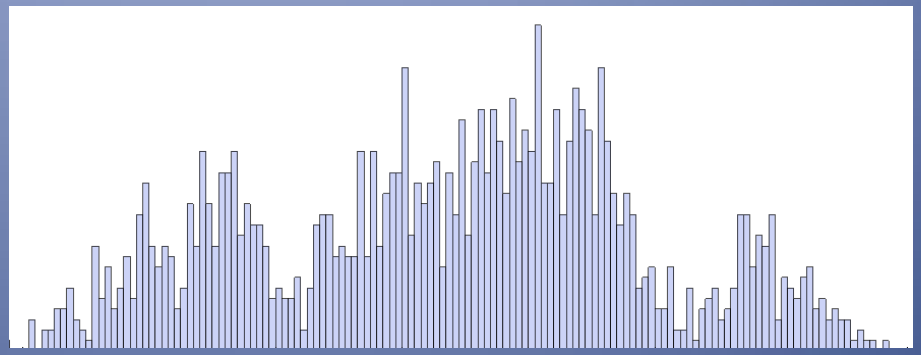


Frequency of (no longer!) bi-stable measurand

Number of bugs

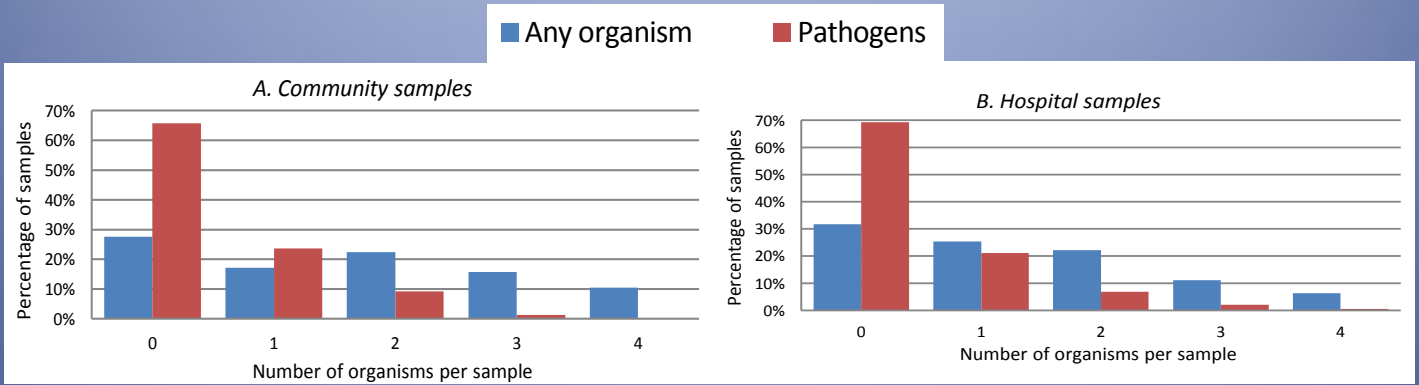
Well ill

Frequency of…
?stochastically generated population frequency



Number of bugs

Species diversity at >10^5 CFU/ml among respiratory samples

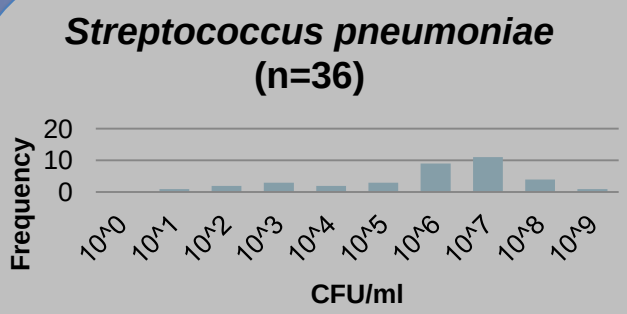


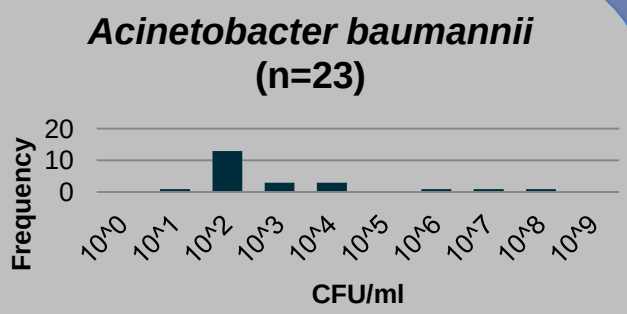
127	Community samples
4.1	Distinct species
2.7	>10^5 CFU/mL
1.6	Pathogens
10%	At least two pathogens at >10^5 CFU/mL

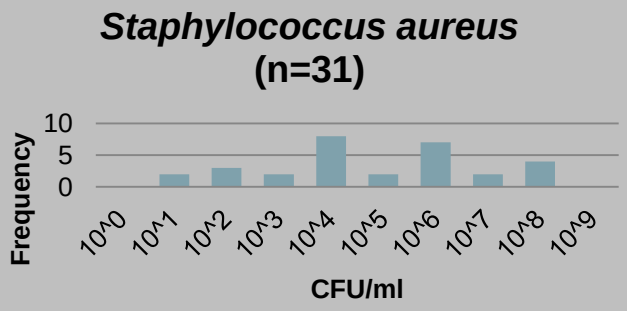
190	Hospital samples
3.1	Distinct species
1.5	>10^5 CFU/mL
1.1	Pathogens
10%	At least two pathogens at >10^5 CFU/mL

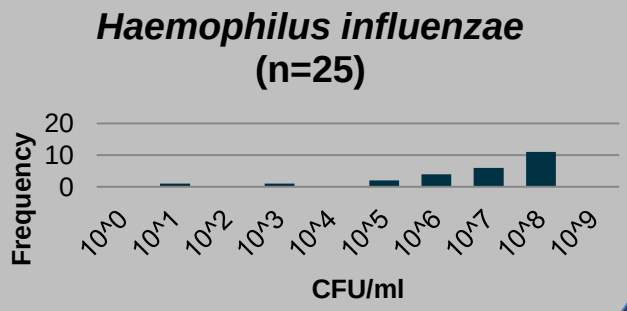
167 sputum; 115 endotracheal tube aspirates; 35 brochoalveolar lavages

CFU analysis of organisms for SPU+ETT (n=302)









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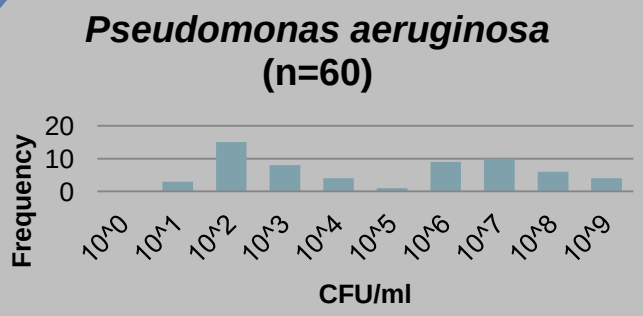
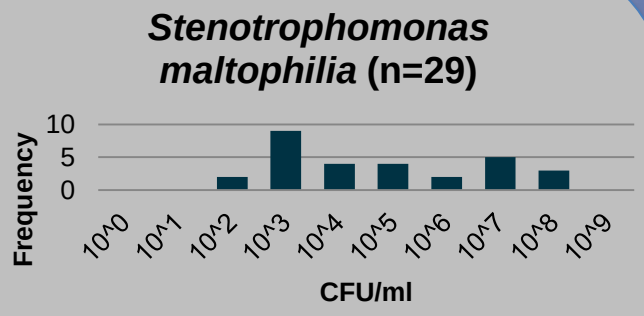
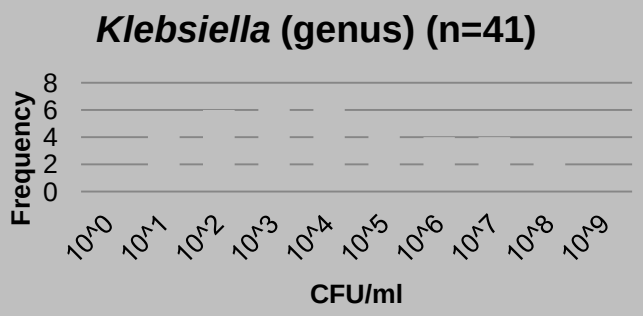
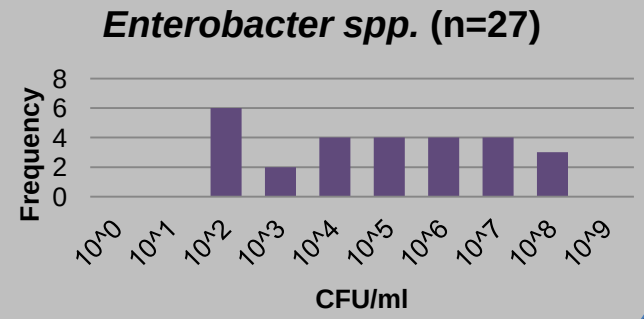








Technical Challenges

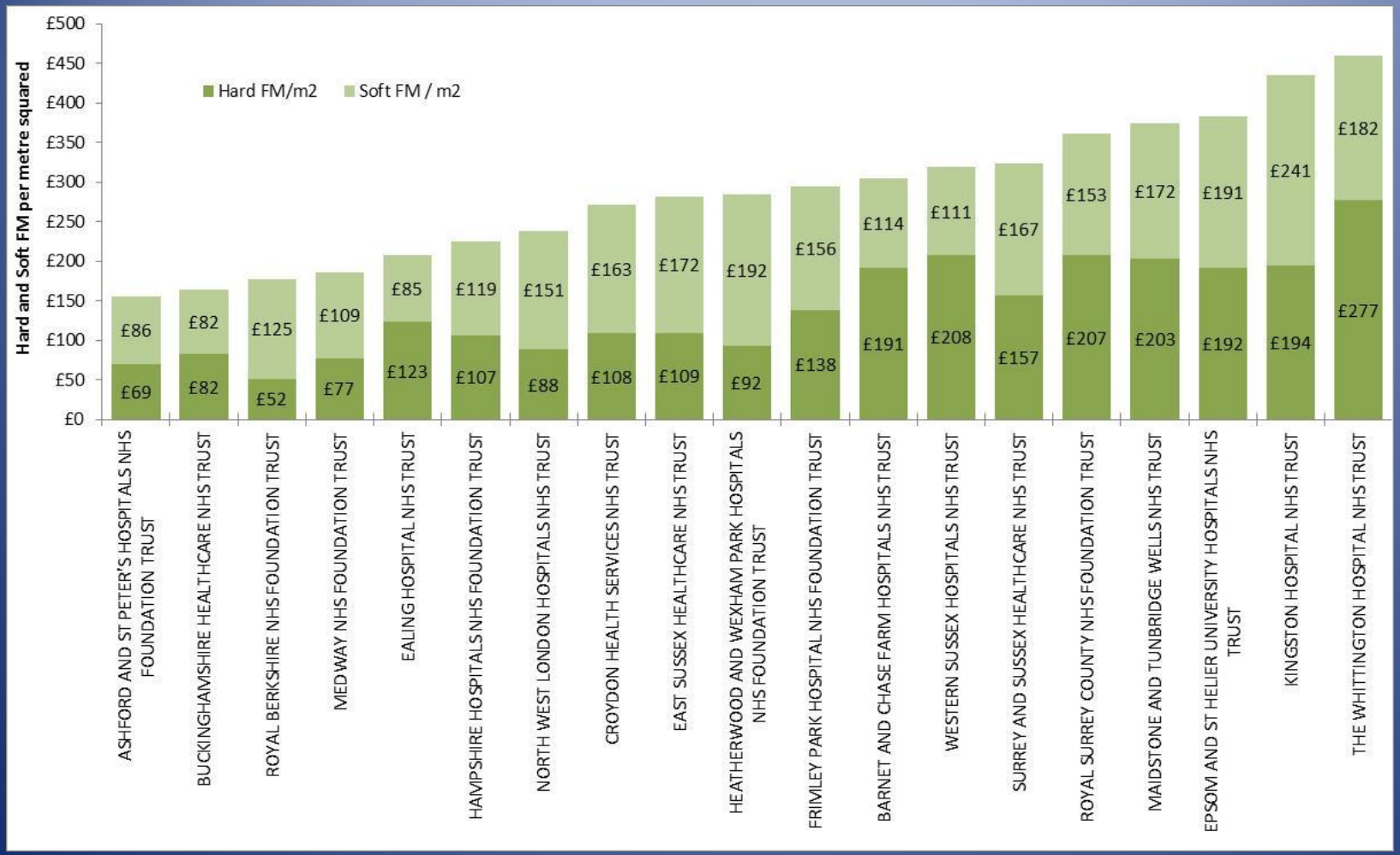
- Distinguishing infection from colonisation
  - Molecular detection potentially much more sensitive than culture
  - **Defining threshold values for qPCR**
- Distinguishing targets between commensal and pathogenic flora
  - Identifying organism for resistance gene carriage
- How to cope with organisms that can be **both** pathogens and commensals
- **How to cope with diversity…???**
- **..and actually – what does this mean…???**

PROBLEM NO. 2: NOT SOLVED.

PROBLEM NO. 3

Space (and money)

In a working NHS laboratory, not far from you…..

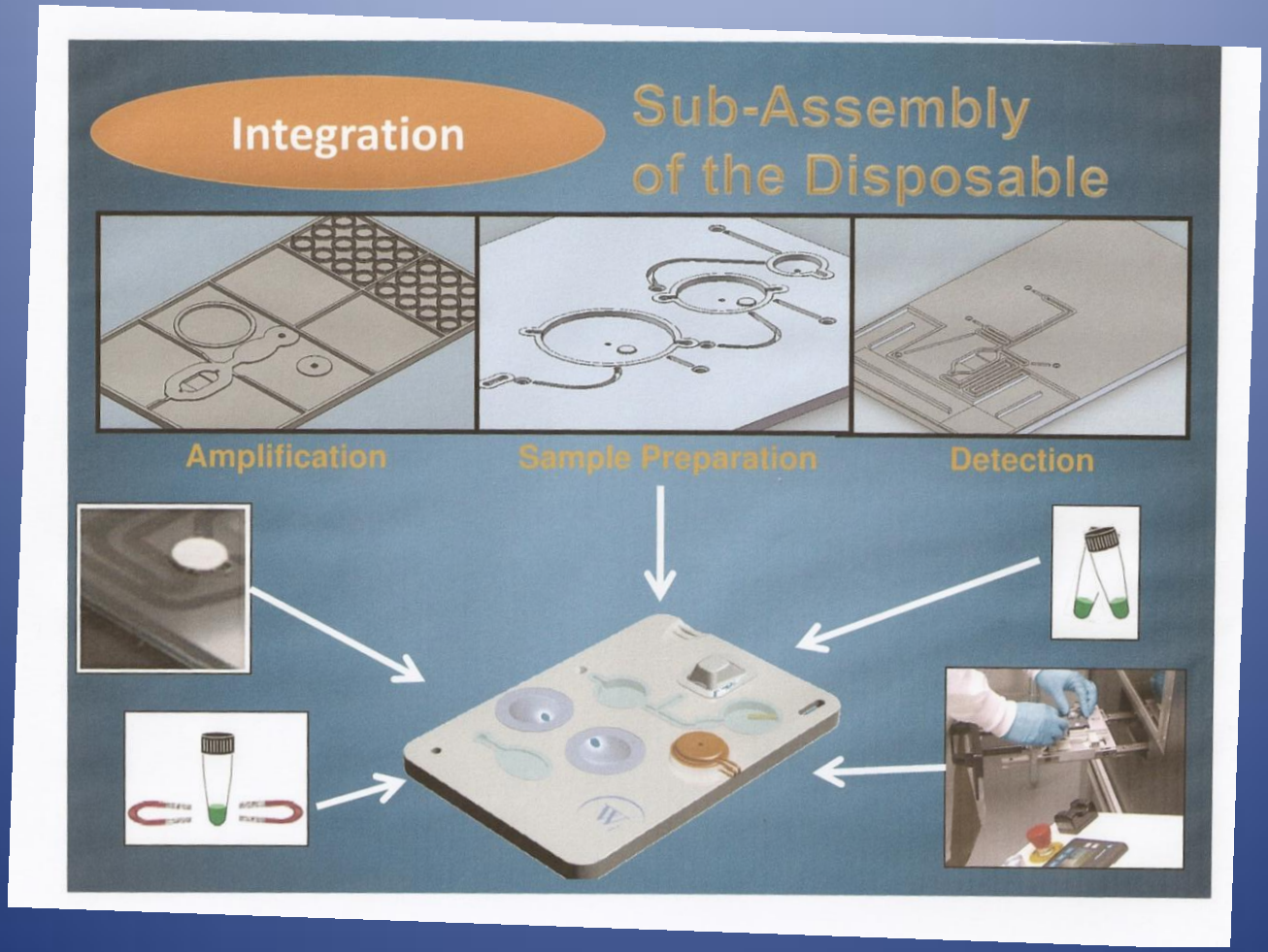


HSL laboratories

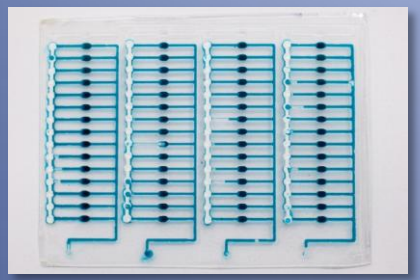
Space: the final (expensive for the NHS) frontier….

Ca. £100 k pa **for the space alone**

The “Lab on a chip” concept

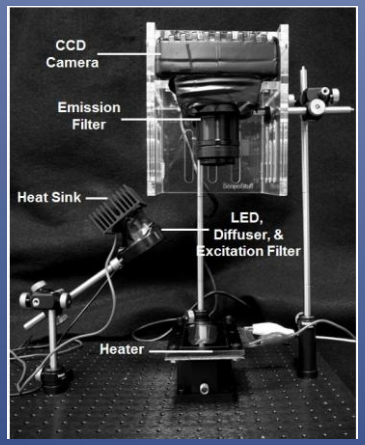


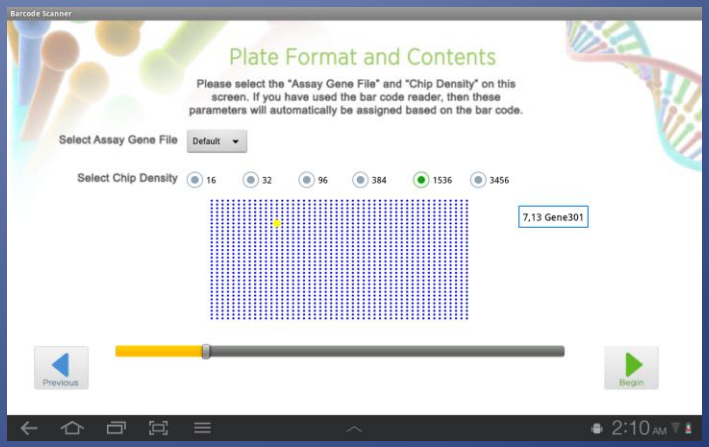
Microfluidic Chips



- 64 wells ~500 nL each
- Chip varies according to the use
- Low cost (material cost < 5 cents per chip)
- Field deployable with minimal training

A Higher Density CCD Based System on Android





Control and Graphical User Interface

OK – it's small – but does it work for patients…??

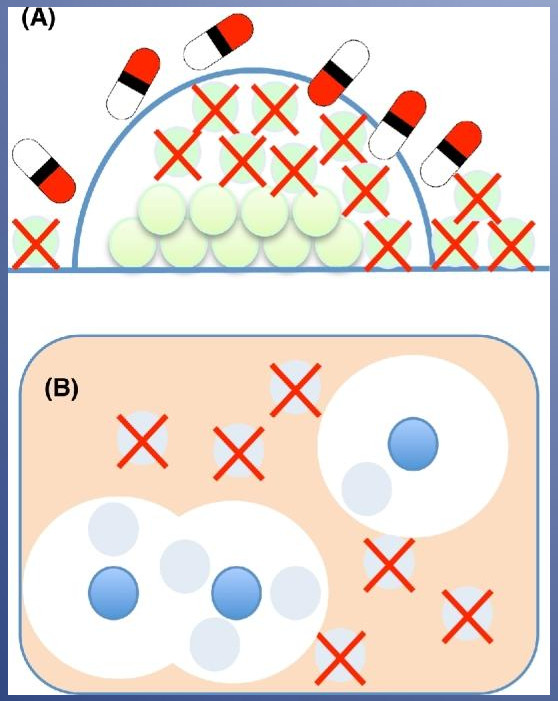
- A reasonable number of small platforms deliver what's on the tin
- These (in general) deliver in clinically actionable timeframes
- Current performance (**independently validated)** evidence base(s) not that prevalent
- And…..

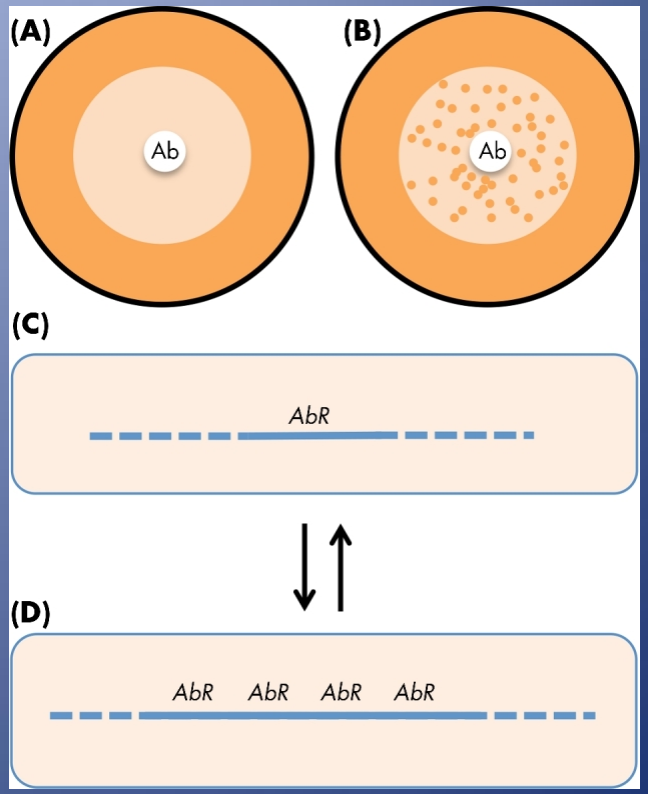
- **Do they make a difference to outcome…..??????**

PROBLEM NO. 3: NOT (RE)SOLVED

PROBLEM NO. 4

Genotype vs. Phenotype



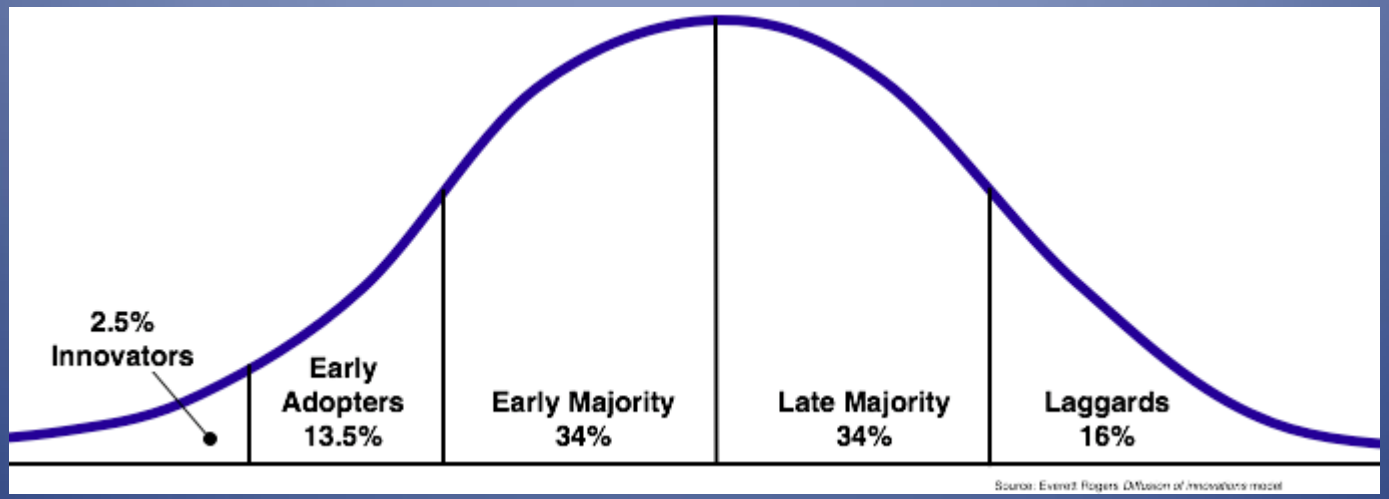


Hughes D, Andersson DI.
Environmental and genetic modulation of the phenotypic expression of antibiotic resistance.
FEMS Microbiol Rev. 2017 May 1;41(3):374-391

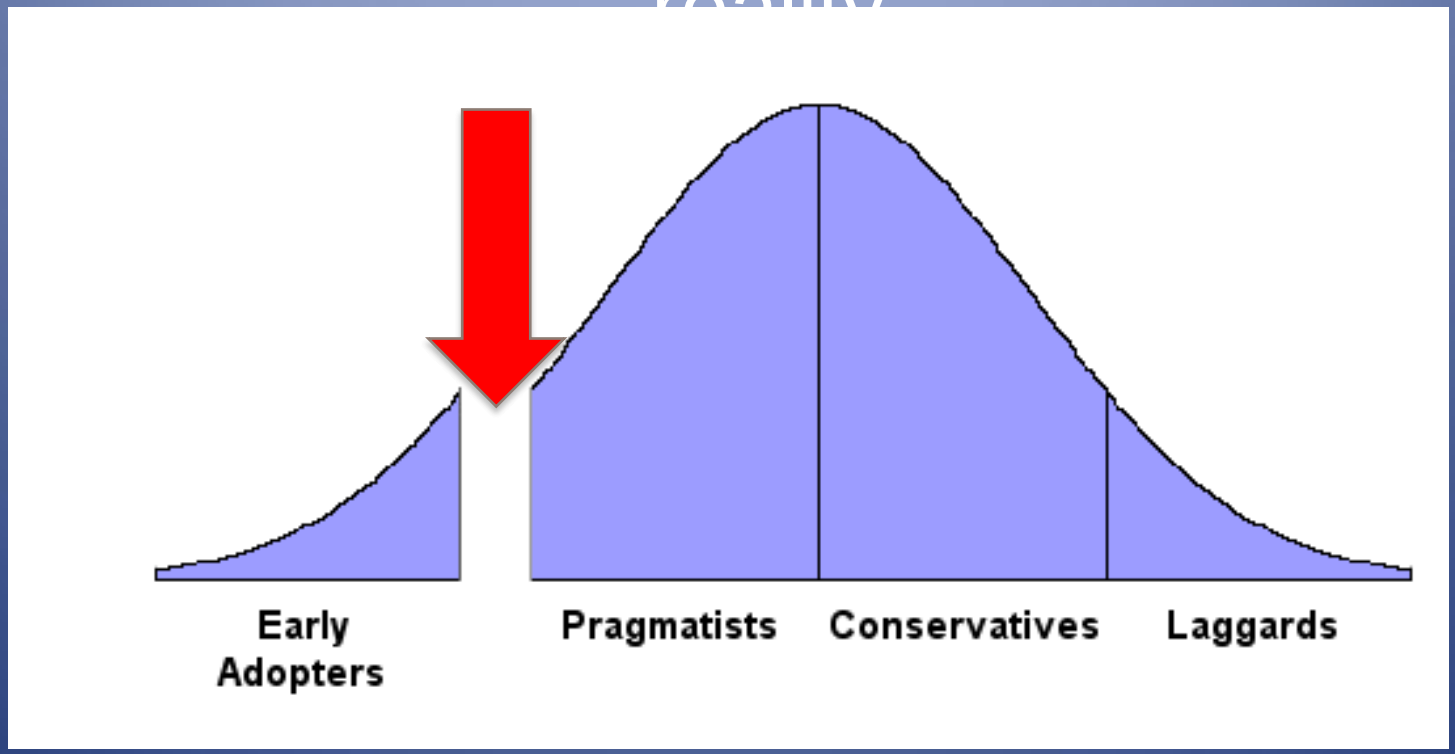
PROBLEM NO. 4: NOT SOLVED (OR PERHAPS SOLVABLE)

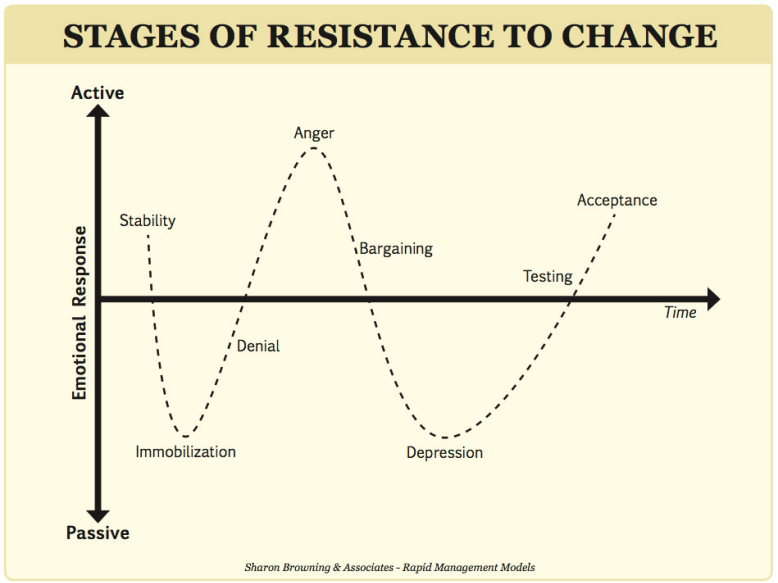
PROBLEM NO. 5

The adoption cycle: theory



The adoption cycle: reality

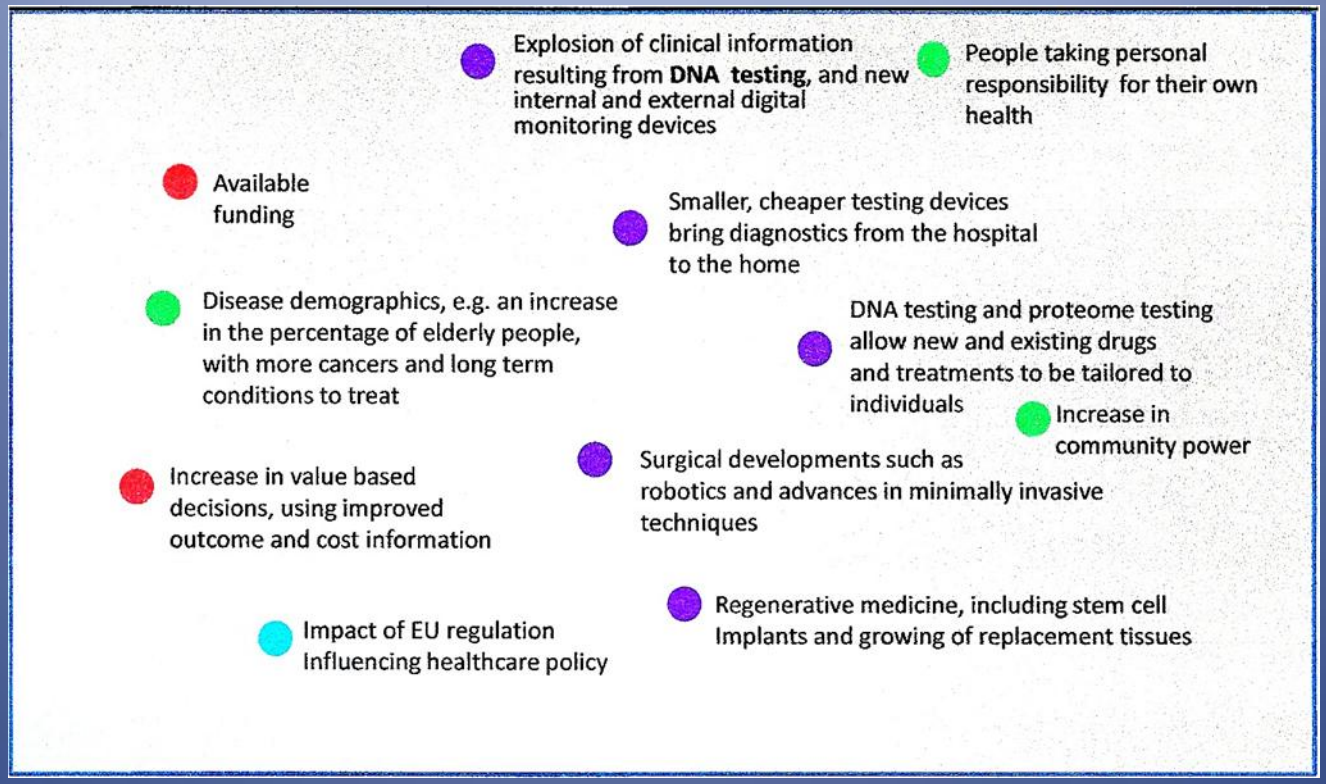




Sir Derek Wanless' report(s) for the NHS

- Improvements to NHS pay and new financial incentives to encourage staff to improve services
- NHS staff must increase productivity from 2% a year at present to 2.5% a year in the first 10 years if improvements are to be made
- A doubling of spending on information technology
- A major increase in the new hospitals building programme to bring the average age of facilities down to 30 years
- **An average of over eleven years from a good idea to its widespread implementation**

PROBLEM NO. 5:
NOTHING SHORT OF SOCIETAL



importance

regulatory

economic

technological

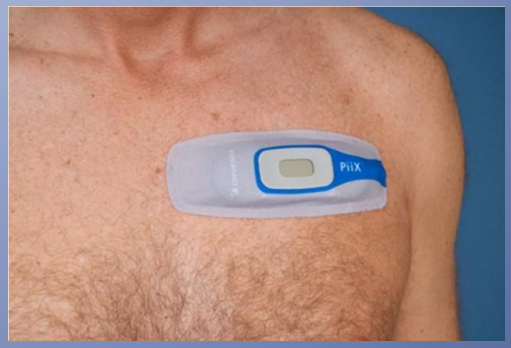
social

Uncertainty

New Pathology = solutions, not test results.

- The technology for finding bugs is not the issue –it's here.
- The technology for finding *relevance* in their presence is beyond PCR.
- The technology for getting *phenotypic* antibiotic resistance right is not here, with a molecular solution only - yet.
- The Price is not the issue – it's the Cost of not having the Solution, and the *perceived* cost of spending to Save.
- Our Central Role in providing diagnostic solutions is often undervalued – despite its central role in Medicine and patient outcomes.

“The Gadget Show”



• Public appetite for affordable healthcare technologies has fuelled a revolution in attitudes towards self- care and Treatment

• Many GPs put out of business as self - diagnosis and treatment becomes common

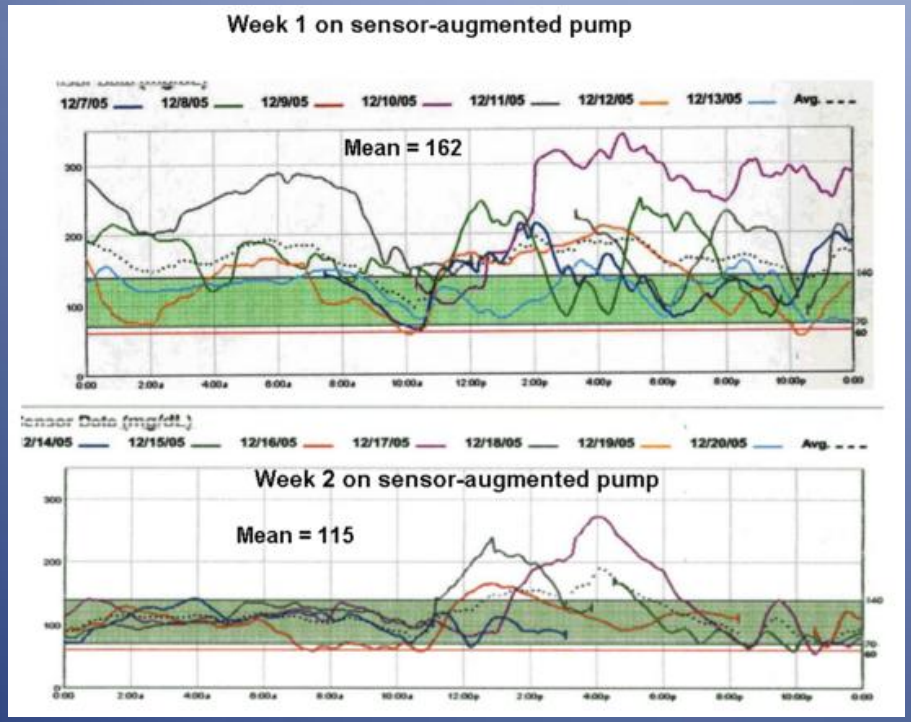
• Centralised specialist acute care, DGHs in decline, only entrepreneurial NHS organisations have survived

• International communication standards allow devices to Communicate – online expertise accessed 24/7

• Private sector provider brands become household names, especially in diagnostics and self
-care

• Elderly and vulnerable unable to embrace new technologies increasingly forgotten

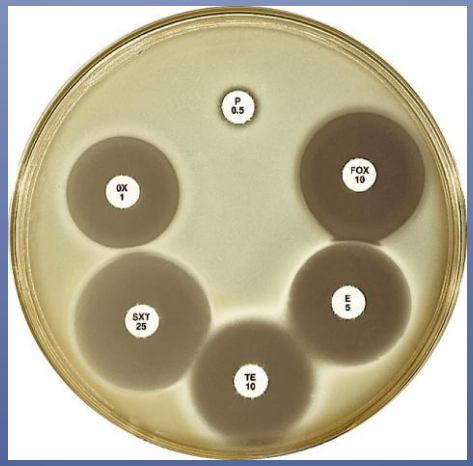
Chris Evenett

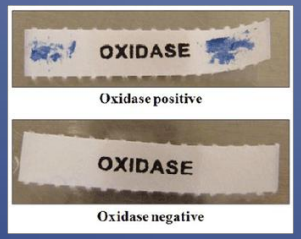


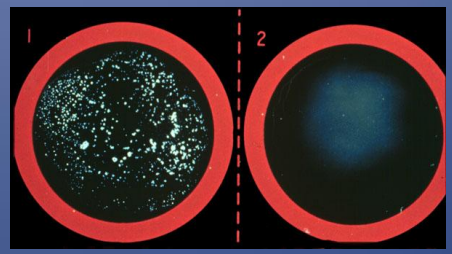
Conclusions

- PCR-based “sample-in/answer-out” technology has potential to considerably increase the speed of diagnosis of bacterial infections, while reducing “hands-on” time
- Number of targets that can be detected is limited – **for now**
- Potential to reduce inappropriate antimicrobial prescribing and improve clinical outcome
- Performance in the clinic yet to be established – will clinicians “trust” the results?

What of the old School?







Then

Yesterday

Now

Acknowledgments